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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,486	06/14/1999	JOHN FRANCIS MARTIN	GJE-30	9834

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,486	MARTIN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9 and 39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/10/06 has been entered.

Claim 43 was added as requested.

Claims 1-6, 8, 9 and 39-43 are pending and under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, 9 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting intimal hyperplasia at a site in a blood vessel in a rabbit, by periadventitial administration at the site of a liposomal composition comprising a DNA expression vector encoding vascular endothelial growth factor (VEGF), does not reasonably provide enablement for

treatment of any vascular disorder in any species other than a rabbit, for DNA delivery compositions other than nucleic acid/liposome complexes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in Paper Nos. 15 and 18.

Claims 1-6, 8, and 9 are drawn to methods of treating or inhibiting intimal hyperplasia. The recited method steps require administration of a nucleic acid encoding human VEGF. The nucleic acid must be delivered periadventitially to a site where intimal hyperplasia is present or may occur. The claims require inhibition or reduction of hyperplasia. In a previous Action, the phrase "whereby intimal hyperplasia of the blood vessel is ... reduced" was interpreted as embracing reversal of existing hyperplasia. However, the specification was carefully reconsidered, and there was no evidence that Applicant wished to embrace reversal of existing hyperplasia by this phrase, but instead focused on inhibiting hyperplasia, i.e. reducing or limiting the extent limiting the extent of hyperplasia. Claims 39-42 are drawn to methods of delivery of a human VEGF protein to a cell of a blood vessel whose endothelium is intact by periadventitial administration of a nucleic acid encoding the human VEGF. The specification discloses no other purpose for performing this method than for inhibiting intimal hyperplasia for the purpose of treating or prevention of stenosis or restenosis. As a result, claims 39-42 face the same enablement issues as claims 1-6, 8, and 9.

The specification teaches a working example in which plasmid expression vectors encoding VEGF were complexed with liposomes and delivered to the adventitial

surface of a rabbit carotid artery underneath a silicone collar. It was previously shown that placement of a silicone collar on a rabbit carotid artery causes intimal hyperplasia. Injection of VEGF plasmid/liposome complexes inhibited intimal hyperplasia, but this inhibition decreased after two weeks, probably due to a loss of transient gene expression. See the specification at page 33, lines 11-22, and page 36, lines 20-26. The specification teaches no example of complete prevention of stenosis or restenosis.

Nucleic acid-mediated therapy

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "[s]ignificant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "[a]though more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "[t]hus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating

that "[t]here is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

With specific respect to therapies based on the transfer of VEGF to the arterial wall, Laitinen (Pharm. Res. 4744): 251-254, 4/1998) taught that although promising effects on cardiovascular diseases have been noted by adventitial delivery of genes in animal models using the collar device disclosed at page 16, lines 21-23 of the specification, "further studies regarding gene transfer techniques, vectors, and safety of procedures are needed before a full therapeutic potential of gene therapy in vascular diseases can be evaluated." See abstract. See also sentence bridging pages 252 and 253, and last sentence of CONCLUSIONS on page 253. Thus the treatment of vascular diseases in general by delivery of VEGF nucleic acids was unpredictable at the time the invention was filed.

Relevance of animal models of intimal hyperplasia to human disease and treatment

The prior art teaches that successful treatment of intimal hyperplasia in small animal models is not predictive of success in other animals, particularly in humans. Muller et al (J. Amer. Coll. Cardiol. 19(2):418-432, 1992) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary

balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. The instant specification teaches a single example of inhibition of intimal thickening at the precise site of VEGF expression vector administration in a rabbit model of intimal hyperplasia. See Example 1, pages 33-38. The specification teaches no example of complete prevention of intimal hyperplasia in any model. With respect to rabbit models, Muller notes that rabbit arteries are not necessarily structurally equivalent to human arteries. For example, the amount of elastin in the media of coronary arteries is less than that in larger mammals, the intima is thinner, and the subendothelial space between the endothelium and the internal elastic lamina is very narrow and virtually acellular. A similar intimal structure is found in the arteries of humans only during fetal and early neonatal life. See paragraph bridging columns 1 and 2 on page 420. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies. See abstract. Also, after reviewing rat, rabbit, dog, non-human primate, and pig models Muller found that it was "clear that there are major differences among the animal models, particularly in terms of the nature of arterial injury and the composition of the neointima. It could be expected, therefore, that a pharmacological therapy that is effective in one animal model may be ineffective in another species or in

humans." See page 426, column 2, first full paragraph. Thus Muller clearly indicates that results in one animal model are not necessarily predictive of results in another animal model due to physiological differences between the models.

Lafont et al (Ann. Card. Ang. 44(7): 349-353, 9/1995), reviewed the results of fifteen years of research prior to 1995, and conclude that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract. Lafont et al (Card. Res. 39(1): 50-59, 7/1998) further indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. In fact, the unpredictability in extrapolating results of such studies to humans was still noted in 1999 after the priority date of the instant application, when Johnson et al taught that small animal models "lacked efficacy in predicting the success of interventions to inhibit restenosis in humans", and found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions. See abstract. Finally, Appleby and Kingston (Current Gene Therapy 4:153-182, 2004) reviewed the state of the art of restenosis gene therapy after the time of the invention. These authors relate that despite promising results from numerous animal studies, there has been a general

failure to obtain similar results in humans. This is primarily due to an incomplete understanding of the vascular biology of restenosis which makes it difficult to select therapeutic genes, dissimilarity between humans and the animal models under study, and difficulty in obtaining localized gene transfer into coronary arteries in vivo. The authors conclude that progress in each area will be required before gene therapy in the vasculature becomes a clinical reality. See abstract and last two paragraphs on page 176. For these reasons, the enabled use of the claimed invention is limited to the treatment of rabbits.

Finally, Bhardwaj et al (Eur. J. Clin. Invest. 35: 669-676, 2005, listing instant inventor Yla-Herttuala as coauthor), using a periadventitial silastic collar, showed that delivery of adenoviral vectors encoding human VEGF A, VEGF D, or VEGF $D^{\Delta N \Delta C}$ induced intimal hyperplasia in carotid arteries in a rabbit model. See page 673 column 2, lines 4-14 of discussion, reproduced below:

Here, it was shown that adenovirus-mediated VEGF-A, VEGF-D and VEGF-$D^{\Delta N \Delta C}$ gene delivery to adventitia produced significant increases in neointima formation in the transduced carotid arteries. It should be noted that gene transfer in the collar model was accomplished by an extravascular approach that did not involve direct injuries to the endothelial lining of the artery [citation omitted].Thus, unlike intravascular gene transfer approaches after balloon denudation, neointimal formation in the collar model took place under an anatomically intact endothelium. Some members of the VEGF family decreased neointima formation by promoting endothelial regeneration when given through the intraluminal route after balloon denudation [citation omitted]. The disparity in the results from these two different approaches suggests that VEGFs may have different effects in different compartments of the vascular tissue which may, in turn, also differ in damaged and intact arteries. The vascular compartment where the VEGFs are expressed together with their concentration (i.e. plasmid vs. adenovirus-mediated gene delivery) could be crucial in determining their net effects *in vivo* [citation omitted].

Regarding other human VEGFs, Bhardwaj taught that that there was no significant difference between VEGF-B, C, or $C^{\Delta N \Delta C}$ and the lac Z control, suggesting that these VEGFs did not inhibit intimal proliferation associated with the collar model. See page 676 last paragraph, and Fig. 2 on page 673. So, Bhardwaj showed that at

least one isoform of every human VEGF known at the time of filing, as well as human VEGF-D, caused the opposite effect to that which is claimed in the instant application, when expressed via adenoviral vector after periadventitial administration. This is objective evidence that the claimed invention is not enabled for its entire scope. Furthermore, Bhardwaj indicates that any of several factors including the type of vector, the concentration of the expressed product, and the site of delivery (lumenal vs periadventitial) may affect the results of VEGF expression on intimal hyperplasia, and that the role of VEGFs in intimal hyperplasia remains controversial, which is further evidence of the unpredictability of the claimed method. See page 670, column 1, lines 10-12, and page 676, column 1, lines 6-9.

In summary, at the time of the invention the art of gene therapy generally was highly unpredictable; those of skill in the art recognized that one could not accurately extrapolate positive results from small animal models of smooth muscle cell proliferation to other animals, particularly humans; the specification fails to provide guidance that would allow such extrapolation; the specification fails to provide any working example of treatment in any organism other than a rabbit, and the post-filing art provides objective evidence that a portion of the claimed scope of the invention was in fact non-functional. For these reasons, one of skill in the art could not practice the claimed methods commensurate in scope with the claims without undue experimentation.

Response to Arguments

Applicant's arguments filed 4/4/06 have been fully considered but they are not persuasive.

At page 4 of the response, Applicant argues that claims 39-42 are enabled because one of skill in the art would know that these methods need not be used for therapeutic purposes, and could also be used to study the activity of VEGF on the cells of the blood vessel. This is unpersuasive the use of the invention to learn more about how the invention works is not an enabled use, but merely an invitation to perform further research.

In the paragraph bridging pages 4 and 5 of the response Applicant states that the US Food and Drug Administration (FDA) has granted approval to Applicant's to proceed from phase I clinical trials to phase II clinical trials, and argues that FDA, which reviewed Applicants" small animal data, was of the opinion that Applicant's methods warranted approval for human trials. Applicant concludes that FDA found Applicant's small animal data as being reasonably predictive of efficacy in humans. This is unpersuasive for several reasons.

First, the PTO does not know what data the FDA used in approving Applicants' clinical trial. Note that Applicant previously argued that the FDA relied upon data from a pig study using VEGF-D nucleic acids (see page 3, lines 6-11 of the response filed 11/8/05). This study was not available to the public at the time of the invention, and VEGF-D had not even been discovered at the time of the invention, so it is not

persuasive as evidence of either the state of the art at the time of the invention or of enablement of the invention generally.

As Applicant correctly points out, the PTO is not to place itself in the role of the FDA. In fact, the PTO has not done so. Instead, the PTO has performed a Wands analysis, and as part of that analysis established that at the time the invention was filed no restenosis strategies based on inhibition of smooth muscle cell proliferation that successfully limited restenosis in animal models had ever been used to successfully treat intimal hyperplasia in humans. See Lafont (1995) and Lafont (1998) above. As discussed in the rejection, this is because intimal hyperplasia in humans is a physiologically different process taking place in physiologically different structures than in the animal models such as the rabbit.

The fact that animal models are used for research does not mean that the results obtained in these animal models will be applicable to humans, and the evidence of record shows that the results in animal models of intimal hyperplasia both before and after the time of the invention were not applicable to humans. With specific regard to whether or not there is a reasonable correlation between the small animal models and the human disease, the sentence bridging columns 1 and 2 on page 54, and column 52, lines 3-11 of Lafont (1995) is relevant. In this passage Lafont indicates that the usefulness of small animal models lies in providing answers to specific biochemical questions, e.g. determining the mechanism of action of a drug on smooth muscle cell proliferation, while noting that the results should not be interpreted to mean that the drug is also able to inhibit restenosis in man. Lafont concludes that "extrapolation of

animal studies directly to man is ***unreasonable*** given the vast differences between animal models and man and the complexity of the restenotic process." Emphasis added. Thus the utility of animal models of intimal proliferation lies in answering specific biochemical questions, but those of skill in the art appreciate that there is not a reasonable correlation between these models and human disease that would support extrapolation of results from the models to humans. It is also noted that the fact that clinical trials are in progress does not mean that a particular invention is enabled. See Verma (1997) above, who indicated that over 200 gene therapy clinical trials were in progress, but not a single one had met with success.

At pages 5 and 6 of the response, Applicant indicates that the Muller and Lafont references do not definitively state that therapies developed in small animal models must necessarily be ineffective. The Examiner concurs, but notes that these references were not relied upon to establish that the invention could not possibly work. Instead, Muller and Lafont were relied upon to demonstrate the unpredictability in extrapolating to humans results from small animal models of intimal hyperplasia and restenosis. The Muller reference does so by indicating that as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models, but none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. As noted in the rejection, Lafont demonstrates this unpredictability by reviewing the results of fifteen years of research prior to 1995, and concluding that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which

successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract. This unpredictability, combined with the unpredictability of gene therapy, the failure of the specification to provide any working example of treatment in any organism other than a rabbit, the failure of the specification to provide guidance that would allow one to extrapolate small animal model results to humans, and the objective evidence in the post-filing art that a portion of the claimed scope of the invention is non-functional, leads to a finding of a lack of enablement.

Applicant asserts that Lafont (1995) and Muller (1992) do not represent the state of the art with respect to the relationship between small animal models and humans in the treatment of intimal hyperplasia, apparently due to their publication dates. This is unpersuasive because the effective filing date of the instant invention is 11/1/1996, and the post filing art cited in the rejection confirmed that small animal models lacked efficacy in predicting the success of interventions to inhibit restenosis in humans even after the invention was filed. See Lafont (1998), Johnson (1999), and Appleby (2004) above. Applicant did not address these references in the response, and presented no evidence that the state of the art changed between Lafont's 1995 publication date and 11/1/1996.

At page 6 of the response Applicant argues that the PTO has recognized that small animal models are reasonably predictive of outcome in human clinical trials, relying for support on US Patent 5,830,879 to Isner in 1998 with claims directed to methods of inducing reendothelialization of an injured blood vessel in a human.

Applicant states that the only data presented in Isner was obtained using rabbits. This is unpersuasive because inducing reendothelialization of an injured blood vessel is not the same thing as inhibiting restenosis. The Isner patent requires inducing cellular proliferation, whereas the instant claims require inhibition of cellular proliferation. The Office has shown that small animal models of intimal hyperplasia and restenosis are not predictive of the situation in humans. This does not necessarily have any direct bearing on methods of stimulating reendothelialization, so it is unclear how issuance of the Isner patent shows that the PTO recognized that small animal models of restenosis are reasonably predictive of outcome in human clinical trials. Applicant is also reminded that each application is considered on its own merits.

Regarding the breadth of VEGF proteins embraced by the instant claims, Applicant argues that a person of ordinary skill in the art, apprised of the specification, would expect that VEGF-A and VEGF-D could both be used in the claimed methods. However, the standard for enablement under 112, first paragraph is whether one of skill in the art at the time of the invention, could make and use the claimed invention without undue experimentation. As discussed previously, VEGF-D and the gene encoding it were not discovered until 1997 (Yamada et al Genomics 42(3): 483-488), so neither Applicant nor anyone else of record was in possession of nucleic acids encoding VEGF-D at the time of the invention. It follows that one of skill in the art at the time of the invention could not have used nucleic acids encoding VEGF-D for any purpose without undue experimentation.

Finally, Applicant discusses the Declaration of Dr. Martin from 11/25/02, indicating that issues of statistical significance, sample size, and the appearance that the method actually resulted in an increase in intimal hyperplasia over time, are irrelevant. Applicant employs an analogy to cancer treatment, arguing that a treatment for cancer is still a treatment even if it only results in a remission that is followed by disease recurrence. This is unpersuasive for several reasons.

First, the experiment in the Declaration was conducted using VEGF-D nucleic acids. As indicated above, these nucleic acids were not in Applicant's possession at the time of the invention because they were not discovered until 1997. So, results obtained with them can have no relevance to the enablement of the claimed invention.

Second, Applicant's analogy is flawed because the Declaration states that "at day 60, it was noted that there was an increased degree of intimal proliferation/fibrosis and a reduction in luminal diameter in the groups which received VEGF adenovirus, when compared to the two control groups, and that luminal occlusion was seen only in animals treated with VEGF-D." This is not analogous to a recurrence of cancer after remission. This is analogous to a treatment causing cancer. Note that this is also consistent with Bhardwaj (2005) who found that periadventitial administration of adenoviruses encoding VEGF-D caused an increase in intimal hyperplasia, and not a decrease.

Third, the size of the sample and statistical treatment of the data allow one to judge its significance. If the data show no significant difference between control and experimental groups, then they do not reflect operability of the invention and do not

support patentability. So, even if the results had been obtained using a VEGF that was available at the time of the invention, they do not support patentability because it is not clear that they provide any evidence that the invention functions as claimed.

Finally, even if the data were statistically significant, they may be more consistent with treatment causing an increase in intimal hyperplasia instead of a decrease. Intimal hyperplasia is known to occur in about 30% of arterial bypasses after two years (see specification at page 2, lines 10 and 11). The Declaration states that it "is generally accepted that stenosis of less than 50% do not cause hemodynamic changes and are therefore regarded as insignificant in relation to flow restriction." See page 4. The data on page 4 show that in the group of animals showing the greatest response to treatment, half had greater than 50% restenosis, and half had less than 50% restenosis. This is interpreted as restenosis occurring in one half of the treated group. However, if restenosis generally occurs in only 30% of patients, then this result would seem either insignificant or reflective of an actual increase in the frequency of intimal hyperplasia. Note again that an increased level of intimal hyperplasia is consistent with the report of Bhardwaj (2005), discussed above.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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